

Docket No. 17668-A7-B/JPW/GJG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Richard Axel et al.

Serial No.: 08/484,136

Examiner: J. Ketter

Filed : June 7, 1995

Group Art Unit: 1636

For : METHOD OF PRODUCING PROTEINACEOUS MATERIALS

1185 Avenue of the Americas
New York, New York 10036
June 14, 2001

Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

SECOND SUBMISSION UNDER 37 C.F.R. § 1.129(a) AND
AMENDMENT IN RESPONSE TO OCTOBER 24, 2000 FINAL OFFICE ACTION

This is Applicants' Second Submission under 37 C.F.R. § 1.129(a) and a response to the final Office Action issued October 24, 2000 in connection with the above-identified application. This Second Submission is being filed concurrently with a Communication Requesting Withdrawal Of Finality Under 37 C.F.R. § 1.129(a).

Please amend the subject application as follows:

In the Claims

Please amend claims 126, 130 and 131, and cancel claim 135 under 37 C.F.R. § 1.121(c). The amendments to claims 126, 130 and 131 are shown in the marked up version of claims 126, 130 and 131 attached hereto. All of the pending claims are presented below.

g. 126. (Amended) A DNA construct for expression in eucaryotic cells comprising DNA I encoding a proteinaceous material foreign to such eucaryotic cells and linked thereto DNA II encoding an amplifiable dominant selectable phenotype not expressed by such eucaryotic cells prior to transformation

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with the construct, the construct being effective for producing the proteinaceous material when the construct is introduced into such ~~in~~ eucaryotic cells.

127. A DNA construct of claim 126 for expression in mammalian cells.

128. A DNA construct of claim 127 for expression in Chinese Hamster Ovary cells.

129. A DNA construct of claim 126, wherein the proteinaceous material is an interferon, insulin, a growth hormone, a clotting factor, a viral antigen, an antibody, or an enzyme.

130. (Amended) A DNA construct of any of claims 126-129, wherein DNA II encodes a dihydrofolate reductase which renders such eucaryotic cells resistant to methotrexate.

131. (Amended) A DNA construct for expression in Chinese Hamster Ovary (CHO) cells comprising DNA I encoding a proteinaceous material foreign to such CHO cells and linked thereto DNA II encoding a dihydrofolate reductase which is not expressed by such CHO cells and renders such CHO cells resistant to methotrexate when the CHO cells are transformed with the construct, the construct being effective for producing the proteinaceous material when the construct is introduced into such CHO cells.

133. The DNA construct of claim 126 for expression in plant cells.

134. The DNA construct of claim 126 for expression in yeast cells.

Please cancel claim 135 without prejudice.

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Please add new claims 136-158 under 37 C.F.R. § 1.121(c) as follows:

136. (New) The DNA construct of claim 126, wherein the proteinaceous material is a glycoprotein.

33 137. (New) A transformed eucaryotic cell comprising the DNA construct of claim 126 stably incorporated into the chromosomal DNA of the transformed eucaryotic cell.

sub
Dhr 138. (New) A transformed plant cell comprising the DNA construct of claim 133 stably incorporated into the chromosomal DNA of the transformed plant cell.

139. (New) A transformed mammalian cell comprising the DNA construct of claim 127 stably incorporated into the chromosomal DNA of the transformed mammalian cell.

140. (New) A transformed Chinese Hamster Ovary cell comprising the DNA construct of claim 128 stably incorporated into the chromosomal DNA of the transformed Chinese Hamster Ovary cell.

141. (New) A method of producing a proteinaceous protein which comprises culturing transformed cells of any of claims 137-140 under suitable conditions to produce the proteinaceous material and recovering the proteinaceous material so produced.

142.³ (New) A transformed Chinese Hamster Ovary (CHO) cell which comprises amplified foreign DNA I encoding a proteinaceous material and amplified DNA II encoding a dihydrofolate

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reductase not expressed by the transformed CHO cell prior to transformation, both DNA I and DNA II being stably incorporated into the chromosomal DNA of the transformed CHO cell.

143.⁴ (New) The transformed Chinese Hamster Ovary cell of claim 142,³ wherein the proteinaceous material is a glycoprotein.

144.⁵ (New) A transformed Chinese Hamster Ovary (CHO) cell which comprises amplified foreign DNA I corresponding to a gene of interest which encodes a proteinaceous material and amplified DNA II encoding a dominant selectable phenotype not expressed by the transformed cell prior to transformation, DNA I or DNA II or both being attached to bacterial plasmid DNA or phage DNA, and both DNA I and DNA II being stably incorporated into the chromosomal DNA of the transformed cell.

145. (New) The transferred CHO cell of claim 144, wherein DNA II encodes a dihydrofolate reductase which renders the transformed CHO cell resistant to methotrexate.

146.¹⁴ (New) A method of producing a proteinaceous protein which comprises culturing transformed CHO cells of claim 144⁵ under suitable conditions to produce the proteinaceous material and recovering the proteinaceous material so produced.

147.¹⁵ (New) The method of claim 146,¹⁴ wherein the proteinaceous material is glycoprotein.

148. (New) The transferred Chinese Hamster Ovary cell of claim 144, wherein the DNA I is attached to bacterial plasmid

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DNA.

149. (New) The transferred Chinese Hamster Ovary cell of claim 144, wherein the DNA II is attached to bacterial plasmid DNA.

150. (New) The transferred Chinese Hamster Ovary cell of claim 144, wherein both DNA I and DNA II is attached to bacterial plasmid DNA.

151. (New) The transferred Chinese Hamster Ovary cell of claim 144, wherein the DNA I is attached to phage DNA.

152. (New) The transferred Chinese Hamster Ovary cell of claim 144, wherein the DNA II is attached to phage DNA.

153. (New) The transferred Chinese Hamster Ovary cell of claim 144, wherein both DNA I and DNA II is attached to phage DNA.

154. (New) A transformed Chinese Hamster Ovary (CHO) cell which comprises amplified foreign DNA I corresponding to a gene encoding a glycoprotein of interest and amplified DNA II encoding a dominant selectable phenotype not expressed by the transformed CHO cell prior to transformation, and both DNA I and DNA II being stably incorporated into the chromosomal DNA of the transformed Chinese Hamster Ovary cell.

155. (New) The transformed Chinese Hamster Ovary cell of claim 154, wherein DNA II encodes a dihydrofolate reductase which renders the transformed cell resistant to methotrexate.

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¹⁸
156. The transformed Chinese Hamster Ovary cell of claim ¹⁶154, wherein DNA I or DNA II or both DNA I and DNA II is attached to bacterial plasmid DNA or phage DNA.

¹⁹
157. The transformed Chinese Hamster Ovary cell of any of claims ¹⁶⁻¹⁸~~154-156~~, further comprising the glycoprotein of interest.

¹³
158. The transformed Chinese Hamster Ovary cell of any of claims ⁵⁻¹²~~144, 145 and 148-153~~, further comprising the proteinaceous material.

REMARKS

Claims 126-131 and 133-135 are pending in the subject application.

By this Amendment, applicants have added new claims 136-158.

Support for new claims 136-153 may be found, *inter alia*, in the original claims as filed.

Support for new claims 154-158 may be found, *inter alia*, on page 5, line 3; page 5, lines 16-20; page 10, line 21; page 14, line 24; and page 17, lines 1-6 of the subject specification.

On pages 2-7 of the October 24, 2000 Office Action, the obviousness-type double patenting rejection of pending claims 126-131 has been maintained, and newly added claim 135 has been rejected on the same ground.

On page 8 of the October 24, 2000 Office Action, the rejection of claims 133 and 134 under 35 U.S.C. § 112, first paragraph, based on the assertion that they contain subject matter which was

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/ not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention, has also been maintained.

And on pages 8-9 of the October 24, 2000 Office Action, the rejection of claims 126, 129, 130 and newly added claim 135, under 35 U.S.C. § 112, first paragraph, based on the assertion that the specification, while enabling DNA constructs for expression into mammalian cells, does not reasonably provide enablement for eukaryotic cells other than mammalian cells, has been maintained.

RESPONSE TO REJECTIONS

Obviousness-type Double Patenting Rejection

One Patented Claim Cannot Make Obvious Six Claims

Initially, applicants note that the Examiner has maintained that six claims, 126-131, are obvious from only one patented claim, claim 73 of U.S. Patent 4,399,216. (" '216 patent"). The Examiner justified this by citing M.P.E.P. § 804.II.b.1, and arguing that the specification contains narrower examples supporting the broader claim 73 of the '216 patent, which examples make claims 126-131 obvious.

However, the Examiner has not pointed out precisely which examples are being referred to. More importantly, no showing of motivation been made for selecting the specific elements recited in applicants' claims 126-131 from the specification. For example, mouse cells transformation is disclosed in the subject specification.

Opinions of the CAFC supercede
guidance provided in the M.P.E.P.

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The Examiner then addressed applicants' citation of the *General Foods* case, in part, by referring to the M.P.E.P. Applicants respectfully note that opinions of the Federal Circuit supercede any guidance provided in the M.P.E.P.

The Construct of Claim 126-131 and 133-136 is Not Required to Practice the Invention of Claim 73 of the '216 Patent.

Applicants note that the Examiner has not found support for the concept of linkage occurring after entry into the cell in the '216. However, applicants point out that confirmation of this concept in the '216 patent is not required to support applicants' contention that the construct of claim 126 or 127 is not required to practice the invention of claim 73 of the '216 patent.

As notes previously, claim 73 of the '216 patent, which depends from claim 54 does not require introduction of DNA I linked to DNA II. Claim 54 does not specify at what point in time the linked molecule is formed, whether in the cell or outside the cell. As discussed in the '216, column 6, lines 46-68, DNA I and DNA II can be introduced unlinked, or as discussed in column 7, lines 5-28, DNA I and DNA II can be introduced as one linked molecule. The '216 further notes in column 7, lines 34-36 that either of these two approaches can be used to transfect eucaryotic cells.

Accordingly, and contrary to the assertions in the January 31, 2000 Office Action and again in the October 24, 2000 Office Action, one need not construct the DNA construct of claims 126-131 and 133-136 to practice the invention of claim 73 of the '216 patent. Thus, even if effective patent term extension was a valid basis for an obviousness-type double patenting rejection,

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it would not apply to the instant situation.

The Subcombination/Combination analysis mandates against a finding of obviousness-type double patenting.

Regarding the Examiner's continued use of a combination/subcombination analysis to support the obviousness-type double patenting rejection, applicants point out that the CAFC in the *General Foods* case made it clear that double patenting does not result just because inventions may be characterized as combination/subcombination. Moreover, it is still not clear to applicants precisely what subcombination/combination analysis the Examiner is using. The Examiner merely states that "here, however, in view of M.P.E.P. § 800, the test fails...."

Applicants, on the other hand, have show in their previous responses that following the guideline of M.P.E.P. § 806.05(c) (Rev. 3, July 1997) leads to a conclusion that claim 73 of the '216 patent, the alleged "combination," does not require all of the particulars of the alleged "subcombination", the construct of claims 126-131 and 133-136 for its patentability.

Rejection under 35 U.S.C. § 112, first paragraph
- claims 133 and 134

Regarding the rejection of claims 133 and 134, applicants respectfully point out that page 11, lines 13-24 of the subject specification provides a predicted that their inventive process is applicable to all eukaryotic cells including plant and yeast cells. The applicants' prediction has, in fact, been realized as shown by a number of workers, including U.S. Patent No. 5,866,777, submitted with the previous response. The authors of this patent even state that the '216 patent, which shares a

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common disclosure with the subject application, provides "an efficient process in plant transformation." This is an unambiguous acknowledgment that applicants' work has enabled transformation of eucaryotic cells, including plant cells.

Rejection under 35 U.S.C. § 112, first paragraph
- claims 126, 129, 130 and 135

Regarding the rejection of claims 126, 129, 130 and 135, applicants respectfully submit that claims 126, 129 130 and 135 are enabled for their full scope for the reasons discussed above with respect to claims 133 and 134. Specifically, as noted above, skilled practitioners in the field have confirmed that applicants' inventive method is applicable to all eukaryotic cells, not merely mammalian cells.

New Claims

New claims are not subject to the obviousness-type double patenting rejection for reasons as follow:

-Claims 136, 143, 147, and 154-158 because none of the claims of the '216 make obvious a recitation of "glycoprotein".

-Claims 137-141 because none of the claims of the '216 make obvious a recitation of "linked".

-Claims 142 and 143 because none of the claims of the '216 make obvious a recitation that both DNA I and DNA II are amplified.

-Claims 144-153 because none of the claims of the '216 patent make obvious a recitation of 1) "bacterial plasmid DNA or phage DNA", together with 2) DNA II being amplified.

Conclusion

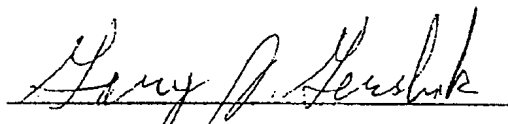
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In view of the preceding remarks, applicants respectfully request the reconsideration and withdrawal of the rejections and objections set forth in the October 24, 2000 Office Action.

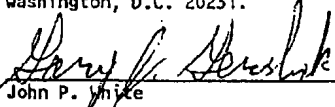
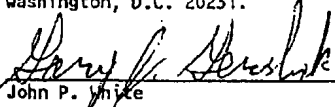
If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed \$710.00 fee for a Submission under 37 C.F.R. § 1.129 is deemed necessary in connection with the filing of this Submission. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.	
 John P. White Reg. No. 28,678 Gary J. Gershik Reg. No. 39,992	 Date 6/14/01

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**Marked-Up Version of Amended
Claims Pursuant to 37 C.F.R. §1.121(c)**

126. (Amended) A DNA construct for expression in eucaryotic cells comprising DNA I encoding a proteinaceous material foreign to such eucaryotic cells and linked thereto DNA II encoding an amplifiable dominant selectable phenotype not expressed by such eucaryotic cells prior to transformation with the construct, said the construct being effective for ~~expressing said producing the~~ proteinaceous material when the construct is introduced into such ~~in~~ eucaryotic cells ~~into which it is introduced.~~
130. (Amended) A DNA construct of any of claims 126-129, wherein DNA II encodes a dihydrofolate reductase which renders ~~transformed~~ such eucaryotic cells resistant to methotrexate.
131. (Amended) A DNA construct for expression in Chinese Hamster Ovary (CHO) cells comprising DNA I encoding a proteinaceous material foreign to such CHO cells and linked thereto DNA II encoding a dihydrofolate reductase which is not expressed by such CHO cells and renders such CHO cells resistant to methotrexate when the CHO cells are transformed with the construct, said the construct being effective for ~~expressing said producing the~~ proteinaceous material ~~in Chinese Hamster Ovary cells into which it~~ when the construct is introduced into such CHO cells.